SHORT PAPER

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A new route to 2,3-dihydro-1,5-benzothiazepines from nitrodisulfides and α,β-unsaturated ketones By SmI_2†

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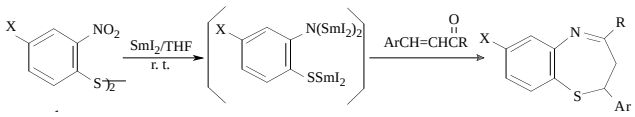
Nitrodisulfides on treatment with SmI_2 in anhydrous THF at room temperature lead to reactive intermediates, which are "living" double-anions and react smoothly with α,β-unsaturated ketones to afford 2,3-dihydro-1,5-benzothiazepines in good yields under mild and neutral conditions.

1,5-Benzothiazepine derivatives are very important and useful compounds in organic and pharmaceutical chemistry. Krapcho and Yale[1] reported that some derivatives have therapeutic activity as central nervous system depressants, ataractic agents and antispasmodics. Recently 1,5-benzothiazepine derivatives can be used as antihypertensive drugs[2] or anticonvulsant agents.[3] The methods for synthesis of 1,5-benzothiazepine from *o*-aminothiophenol and α,β-unsaturated ketones[4] or chalcones[5] have been studied extensively. 1,5-Benzothiazepine derivatives can be also produced by one pot synthesis from *o*-aminothiophenol, ω-bromoacetophenones and aromatic aldehydes.[6] However most of above methods involve harsh conditions such as the use of acid or base catalysts, moderate to high thermal conditions as well as long reaction times.

Samarium diiodide (SmI_2) has evolved as an exceedingly reliable, mild, neutral, selective and versatile single electron reducing agent for promoting reductive reaction difficult to accomplish by other existing methodologies. Its extensive application in organic synthesis has been reviewed in the past decade.[7] The reduction of nitro groups[8] and reductive cleavage of S–S, Se–Se, Te–Te bonds[9] by SmI_2 have been studied extensively. However, to our knowledge, the simultaneous reduction of more than one group by SmI_2 has not been reported in the literature. Herein we describe our preliminary results on the simultaneous reduction of the nitro group and the S–S bond in nitrodisulfides by SmI_2 and its use in the synthesis of 2,3-dihydro-1,5-benzothiazepines (Scheme 1).



Scheme 1

We found that when nitrodisulfides **1** were treated with SmI_2 at room temperature, the deep blue colour of the solution turned into yellow within several minutes. The above appearance showed the nitro groups had been reduced and the S-S bonds had been reductively cleaved simultaneously by SmI_2; the active intermediates **2** were formed at the same time. Although the detailed mechanism of this reaction has not been clarified, according to the relevant literature,[9,10] we consider that the intermediates **2** are "living" double-anion species generated *in situ*. These anionic species react smoothly with α,β-unsaturated ketones at room temperature to afford 2,3-dihydro-1,5-benzothiazepines **3** in good yields. The results are summarized in Table 1. It is apparent from Table 1 that chalcones are more active to react with the new anion species **2** than any other α,β-unsaturated ketones.

Table 1 Synthesis of 2,3-dihydro-1,5-benzothiazepines by SmI_2

Entry	X	Ar	R	T(h)	Yield(%)[a]
3a	H	C_6H_5	Ph	2	78
3b	H	*p*-ClC_6H_4	Ph	3	72
3c	H	*p*-$CH_3C_6H_4$	Ph	2	83
3d	H	*p*-$CH_3OC_6H_4$	Ph	2	84
3e	H	3,4-$(OCH_2O)C_6H_3$	Ph	3	75
3f	H	C_6H_5	Me	3	68
3g	Cl	C_6H_5	Ph	3	72
3h	Cl	*p*-ClC_6H_4	Ph	4	67
3i	Cl	*p*-$CH_3C_6H_4$	Ph	4	71
3j	Cl	*p*-$CH_3OC_6H_4$	Ph	4	65
3k	Cl	3,4-$(OCH_2O)C_6H_3$	Ph	4	82
3l	Cl	C_6H_5	PhCH=CH	12	52

[a]Isolated yield based on nitrodisulfides.

In summary, a new route to 2,3-dihydro-1,5-benzothiazepines has been developed, the advantages of which are the accessibility of the starting materials, simple and mild reaction conditions, convenient manipulation and good yields.

Experimental

General: Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points were uncorrected. Infrared spectra were recorded on IR-408 spectrometer in KBr. ^1H NMR spectra were recorded on Bruker AC–80 spectrometer as $CDCl_3$ solutions. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on HP 5989B MS spectrometer. Microanalysis was carried out on a Carlo-Erba 1106 instrument.

General procedure for the preparation of 2,3-dihydro-1,5-benzothiazepines: a solution of nitrodisulfides **1** (0.5 mmol) in anhydrous THF (3 ml) was added dropwise to 7 mmol SmI_2 in dry THF (30 ml) at room temperature. The deep blue colour of the mixture changed to yellow within several minutes. Then α,β-unsaturated ketones (1 mmol) in THF (2 ml) were added to this solution. After stirring for a given time (Table 1, the reaction was monitored by TLC), the reaction was quenched with dilute HCl (0.1mol/L, 3 ml) and extracted with ether (3×30 ml). The combined extracts were washed with saturated solution of $Na_2S_2O_3$ (15 ml), saturated brine (15 ml), and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative thick layer chromatography using ethyl acetate and cyclohexane (1 : 7) as eluant.

3a, *2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine:* pale yellow crystals, m.p. 112–114°C (lit.,[5a] 114–115°C). ν_{max}/cm^{-1} 1610–1590(C=N), 758(C-S). δ_H 8.06–6.86(14H, m), 4.90–4.45(1H, m), 3.10–2.45(2H, m).

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

3b, *2-(4'-chlorophenyl)-2,3-dihydro-4-phenyl-1,5-benzothiazepine:*[5b] light yellow crystals, m.p. 133–135°C. ν_{max}/cm^{-1} 1613–1592(C=N), 762(C–S). δ_H 8.04–6.79(13H, m), 4.94–4.50(1H, m), 3.14–2.46(2H, m). *m/z* 363(M^+, 2.2)

3c, *2,3-dihydro-2-(4'-methylphenyl)-4-phenyl-1,5-benzothiazepine:*[5b] pale yellow crystals, m.p. 136–138°C. ν_{max}/cm^{-1} 1605–1584(C=N), 752(C–S). δ_H 7.95–6.75(13H, m), 4.90–4.50(1H, m), 3.38–2.85(2H, m), 2.16(3H, s). *m/z* 329(M^+, 1.8).

3d, *2,3-dihydro-2-(4'-methoxyphenyl)-4-phenyl-1,5-benzothiazepine:*[5b] yellow crystal, m.p. 141–143°C. ν_{max}/cm^{-1} 1617–1594(C=N), 1250(=C–OMe), 748(C–S). δ_H 8.05–6.69(13H, m), 4.96–4.46(1H, m), 3.72(3H, s), 3.10–2.43(2H, m). *m/z* 345(M^+, 1.2).

3e, *2,3-dihydro-2-(3',4'-methylenedioxyphenyl)-4-phenyl-1,5-benzothiazepine:*[5b] pale yellow crystal, m.p. 149–151°C. ν_{max}/cm^{-1} 1610–1590(C=N), 2780, 925, 720(OCH_2O), 753(C–S). δ_H 8.00–6.63(12H, m), 5.73(2H, s), 4.86–4.40(1H, m), 3.05–2.28(2H, m). *m/z* 359(M^+, 2.5).

3f, *2,3-dihydro-4-methyl-2-phenyl-1,5-benzothiazepine:* yellow crystals, m.p. 123–124°C (lit.,[11] 121–123°C). ν_{max}/cm^{-1} 1610–1590(C=N), 2980, 1380(CH_3), 758(C–S). δ_H 7.82–6.74(9H, m), 4.70–4.35(1H, m), 3.10–2.75(2H, m), 2.03(3H, s).

3g, *7-chloro-2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine:* light yellow crystals, mp 132–134°C. ν_{max}/cm^{-1} 1610–1580(C=N), 755(C–S), 740(C–Cl). δ_H 8.07–6.77(13H, m), 4.87–4.57(1H, m), 3.47–2.77(2H, m). *m/z* 349(M^+, 2.0), 248(36), 246(100), 105(67). $C_{21}H_{16}ClNS$ Calcd. C, 72.09; H, 4.61; N, 4.00; Found: C, 72.20; H, 4.53; N, 3.78%.

3h, *7-chloro-2-(4'-chlorophenyl)-2,3-dihydro-4-phenyl-1,5-benzothiazepine:* yellow crystals, m.p. 145–147°C. ν_{max}/cm^{-1} 1610–1580(C=N), 760(C–S), 740(C–Cl). δ_H 8.00–6.70(12H, m), 4.90–4.67(1H, m), 2.62–2.34(2H, m). *m/z* 383(M^+, 1.6), 248(36), 246(100). $C_{21}H_{15}Cl_2NS$ Calcd. C, 65.63; H, 3.93; N, 3.64; Found: C, 65.39; H, 4.04; N, 3.78%

3i, *7-chloro-2,3-dihydro-2-(4'-methylphenyl)-4-phenyl-1,5-benzothiazepine:* light yellow crystals, m.p. 165–167°C. ν_{max}/cm^{-1} 1610–1578(C=N), 760(C–S), 740(C–Cl). δ_H 8.04–6.92(12H, m, ArH), 4.90–4.62(1H, m), 3.14–2.74(2H, m), 2.24(3H, s). *m/z* 363(M^+, 1.9), 221(39), 207(100), 105(35), 77(37). $C_{22}H_{18}ClNS$ Calcd. C, 72.61; H, 4.99; N, 3.85; Found: C, 72.47; H, 5.10; N, 3.62%.

3j, *7-chloro-2,3-dihydro-2-(4'-methoxyphenyl)-4-phenyl-1,5-benzothiazepine:* light yellow crystals, mp 148–150°C. ν_{max}/cm^{-1} 1613–1585(C=N), 1250(=C–OMe), 755(C–S), 740(C-Cl). δ_H 8.02–6.75(12H, m), 4.25–4.05(1H, m), 3.51(3H, s), 3.25–2.85(2H, m). *m/z* 379(M^+, 1.2), 248(19), 246(49), 134(100). $C_{22}H_{18}ClNOS$ Calcd. C, 69.56; H, 4.78; N, 3.69; Found: C, 69.44; H, 4.52; N, 3.51%.

3k, *7-chloro-2,3-dihydro-2-(3',4'-methylenedioxyphenyl)-4-phenyl-1,5-benzothiazepine:* light yellow crystals, m.p. 178–180°C. ν_{max}/cm^{-1} 2780, 925, 720(OCH_2O), 1615–1580(C=N), 760(C–S), 740(C-Cl). δ_H 8.00-6.81(11H, m), 5.77(2H, s), 4.96-4.62(1H, m), 3.36–2.80(2H, m). *m/z* 393(M^+, 4.2), 289(23), 246(25), 149(100). $C_{22}H_{16}ClNO_2S$ Calcd. C, 67.09; H, 4.09; N, 3.56; (Found: C, 67.20; H, 3.92; N, 3.43%.

3l, *7-chloro-2,3-dihydro-2-phenyl-4-styryl-1,5-benzothiazepine:* light yellow crystals, m.p. 102–104°C. ν_{max}/cm^{-1} 1650, 965(C=C), 1615–1582(C=N), 760(C–S), 740(C–Cl). δ_H 8.10–6.70(13H, m), 6.23–5.76(2H, m), 4.53–4.23(1H, m), 3.10–2.53(2H, m). *m/z* 375(M^+, 1.2), 272(16), 270(33), 247(38.6), 245(100). $C_{23}H_{18}ClNS$ Calcd. C, 73.49; H, 4.83; N, 3.73; Found: C, 73.33; H, 4.76; N, 3.57%.

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